

**Eradication of Helicobacter pylori and gastric and oesophageal cancer : a systematic review and meta-analysis of cohort studies**

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# Eradication of *Helicobacter pylori* and gastric and oesophageal cancer: a systematic review and meta-analysis.

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## Abstract (Word count: 209)

***Background:*** *Helicobacter pylori (H. pylori)* is associated with an increased risk of gastric adenocarcinoma and gastric mucosa associated lymphoid tissue (MALT) lymphoma, and a seemingly decreased risk of oesophageal adenocarcinoma. We aimed to assess how eradication therapy for *H. pylori* influences the risk of developing these cancers.

***Methods:*** This was a systematic review and meta-analysis. We searched PubMed, Web of Science, Embase and the Cochrane Library and selected articles that examined the risk of gastric cancer, MALT lymphoma or oesophageal cancer following eradication therapy, compared to a non-eradicated control group.

***Results:*** Among 3629 articles that were considered, 9 met the inclusion criteria. Of these, 8 cohort studies assessed gastric cancer, while 1 randomized trial assessed oesophageal cancer. Out of 12,899 successfully eradicated patients, 119 (0.9%) developed gastric cancer, compared to 208 (1.1%) out of 18,654 non-eradicated patients. The pooled relative risk of gastric cancer in all 8 studies was 0.46 (95% confidence interval 0.32-0.66, $I^2$ 32.3%) favouring eradication therapy. The 4 studies adjusting for time of follow-up and confounders showed a relative risk of 0.46 (95% confidence interval 0.29-0.72, $I^2$ 44.4%).

***Conclusion:*** This systematic review and meta-analysis indicates that eradication therapy for *H. pylori* prevents gastric cancer. There was insufficient literature for meta-analysis of MALT lymphoma or oesophageal cancer.

**Keywords:** Stomach neoplasms, oesophageal neoplasms, Helicobacter pylori, eradication.

## Introduction

*Helicobacter pylori* (*H. pylori*) is a bacterium found in the stomachs of half of the adult human population and is typically acquired during childhood.[1] *H. pylori* is associated with chronic gastritis, peptic ulcer, and gastric cancer, particularly in the presence of its virulence factor CagA.[2] The incidence of gastric cancer is declining, possibly due to the decrease in *H. pylori* prevalence,[3] but is still the 5$^{th}$ most common cancer and the 3$^{rd}$ most common cause of cancer death globally.[4] The overall yearly incidence rates globally are 15.6-18.1 and 6.7-7.8 per 100,000 individuals in men and women, respectively.[5] There are considerable variations in incidence geographically, and half of all cases occur in Eastern Asia.[4] Gastric cancer is typically adenocarcinoma (95%), which is sub-classified into intestinal or diffuse type, both associated with *H. pylori,*[6-8] and mixed type. The intestinal type (54%)[9] develops from a gastric mucosa with chronic gastritis, atrophy, intestinal metaplasia, and dysplasia to invasive adenocarcinoma.[10] For the diffuse type (15%)[9] the carcinogenic pathway is less clear. The remaining adenocarcinomas (32%) are of the mixed type. Gastric mucosa associated lymphoid tissue (MALT) lymphomas are also associated with *H. pylori*.[11] Interestingly, *H. pylori* seemingly *decreases* the risk of oesophageal adenocarcinoma.[12] A possible explanation is that *H. pylori*-related atrophic gastritis reduces gastric acid secretion, which in turn counteracts gastro-oesophageal reflux, a main risk factor for this cancer.[12] The increasing incidence of oesophageal adenocarcinoma might be due to the decreasing prevalence of *H. pylori*.[13] CagA positive *H. pylori* strains might also be associated with an increased risk of oesophageal squamous cell carcinoma.[14] In theory, *H. pylori* eradication should reduce the risk of gastric adenocarcinoma, MALT lymphoma and oesophageal squamous cell carcinoma, and increase the risk of oesophageal adenocarcinoma. However, the available literature is limited. Two previous meta-analyses have indicated a decreased risk of gastric adenocarcinoma, while no meta-analysis has examined MALT

lymphoma or oesophageal cancer.[15,16] We aimed to examine the role of *H. pylori* eradication therapy in the development of gastric adenocarcinoma, MALT lymphoma and oesophageal cancer in a systematic review and meta-analysis.

## Methods

This was a systematic review and meta-analysis analysing the risk of gastric adenocarcinoma, MALT lymphoma and oesophageal cancer after eradication therapy for *H. pylori*. The study was performed according to an a priori established study protocol.

### Exposure and outcome

The study exposure was *H. pylori* eradication therapy. All established eradication regimens were considered eligible. *H. pylori* positive individuals who did not receive eradication, and individuals for whom eradication was unsuccessful, were considered unexposed (non-eradicated). The outcomes were gastric or oesophageal malignancy, where the following histological subtypes were considered for inclusion: adenocarcinoma, squamous cell carcinoma, or MALT lymphoma.[17,18]

### Search strategy and study selection

We conducted a systematic search of the medical literature using PubMed, Web of Science, Embase and the Cochrane Library up until November 2015. There were no restrictions regarding article language or date of publication. Articles were considered eligible if the risk of cancer was evaluated in individuals receiving eradication therapy, compared to a control group that did not receive eradication or in which eradication was unsuccessful. Only studies describing a population representative of the general population or representative of individuals receiving *H. pylori* screening and treatment in clinical practice were considered

eligible. The following search terms were used : '*Helicobacter pylori'*, '*campylobacter'*, 'eradication', 'chemoprevention', 'oesophageal neoplasms', 'oesophageal', 'stomach neoplasms', 'gastric', 'cancer', 'carcinoma', 'tumour', 'adenocarcinoma', 'malignancy' (taking into account both British and American spelling), and the names of different medications used for *H. pylori* eradication. A detailed search description can be found in the supplementary documents (Appendix). The results of the search were first evaluated based on article titles by one researcher (ED). The next step of the search was performed by two independent researchers (ED and NB), who evaluated the abstracts and full texts of the remaining articles. Any disagreement between the researchers was solved by consensus. Initial exclusion criteria were animal studies, studies without original data (including commentaries and editorials), meeting abstracts, case reports, and case-control studies. The latter were excluded to maintain comparability of measures of effect. Furthermore, we applied backwards and forward citation tracking (sources cited in included articles and identifying articles that cited the included articles) to all included articles, to identify other possible relevant studies. For studies that reported cancer development after eradication therapy for *H. pylori*, but did not report the number of cancer cases in the control group, we contacted the authors to provide these data to be able to include these articles. When we found multiple articles based on the same study population, we included only the most recent article (with the longest follow-up).

**Data extraction and quality assessment**

Data extraction on cancer development was performed independently by two researchers (ED and NB), who extracted both unadjusted data (i.e. absolute numbers) and adjusted data while taking into account the follow-up time (from Cox or Poisson models). The following data were extracted for each study: geographical location, method to detect *H.*

*pylori*, *H. pylori* eradication regimen, success of eradication, age (mean and range), sex ratio, follow-up time, and the histological type of the cancer.

Two researchers (ED and NB) independently assessed the quality of the studies according to the Newcastle Ottawa scale.[19] The quality of each study was assessed by the following items: representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of the exposure, demonstration that the outcome of interest was not present at the onset of the study, comparability of study cohorts on the basis of the design or analysis, assessment of outcome, length and adequacy of the follow-up of the cohorts. Studies with a score ≤3 were considered of low quality, 4 and 5 of moderate quality, while a score ≥6 defined good quality.

**Data synthesis and statistical analysis**

For the pooled analyses we used a random effect model to take heterogeneity within and between studies into account. *H. pylori* eradication was compared to no eradication or unsuccessful eradication and expressed as unadjusted risk ratios (RR) with 95% confidence intervals (95% CI) for the development of cancer. A second analysis was used to pool the adjusted RR and 95% CI, taking into account follow-up time, in which the adjusted (full model) reported hazard or incidence ratios were used. To assess heterogeneity we used the $I^2$ statistic, where an $I^2$ of >50% was used to define a substantial degree of heterogeneity. Subgroup analyses were performed for baseline gastric histology and type of control group to investigate possible explanations for any heterogeneity. A funnel plot and Egger's test were conducted, where a large p-value (>0.05) indicated no evidence of small study effects or publication bias. The statistical analyses were performed using the statistical software Stata (Stata Corporation, version 12.1).

## Results

### Study selection

The systematic search identified 3629 unique articles (Figure 1). After screening of the titles and abstracts, the full texts of 38 articles remained for further evaluation of eligibility. None of these studies assessed the risk of MALT lymphoma and only one study assessed the risk of oesophageal cancer.[20] Four studies were excluded because of the design; 1 was a case-control study,[21] and 3 others were comments without original data.[22-24] Three studies were excluded because they were reviews or gave notice of an ongoing study and thus contained no new data.[25-27] Other studies were excluded for various reasons as shown in Figure 1.[28-31] Nine studies were randomized controlled trials (RCTs) already described in the most recent meta-analysis,[20,32-39] and no new RCTs were identified after that meta-analysis.[15] After this evaluation of the literature, we restricted our study to cohort studies when examining gastric cancer. Seven other articles were excluded because no suitable control group was described,[40-44] or the risk of cancer was not reported in the control group, nor retrieved after contacting the authors.[45,46] Four other articles described the cancer risk based on the same population,[47-50] so only the most recent article with the longest follow-up was included.[50] After this review, eight observational studies assessing the risk of gastric cancer were selected for final analysis.[50-57] One study, a randomized clinical trial, assessing the risk of oesophageal cancer was included.[20]

### Study characteristics

Patient characteristics for the eight studies examining gastric cancer are presented in Table 1. Seven of the studies were conducted in Japan and one in Finland. Five studies compared successful with unsuccessful eradication attempt,[50-54] and three studies compared eradicated individuals with untreated individuals with *H. pylori*.[55-57] The age

range was 17 to 83 years,[50] with mean ages between 50[50] and 63 years.[56] Most studies included more men than women (Table 1), particularly in one of the studies on factory workers (98% men).[55] Three studies described the baseline gastric histopathology of the patients, while the other five did not. In one study, all patients (100%) had gastric atrophy,[50] and in another study only 5-7% had atrophic gastritis.[52] One study included patients with intestinal metaplasia and a large (undefined) proportion of participants presented with atrophy at baseline.[57] None of the studies included patients with dysplasia or early gastric cancer at baseline. Table 2 describes the eradication therapies used. Success of eradication was measured in five out of eight studies, and the success rate varied between 65%[54] and 87%.[55] Gastric cancer development and follow-up of patients is described in Table 3. The mean follow-up time ranged from 2.9 years[52] to 10.9 years.[51] The majority (up to 89%) of the cancers in both treatment and control groups were intestinal type gastric adenocarcinomas. In the treatment group in one study[50] and the control group of another study[54] there were similar proportions of diffuse and intestinal type adenocarcinomas.

**Quality assessment of included studies**

Of the eight studies, seven were considered of good quality[50-55,57] and one of moderate quality.[56] All studies included a control group from the same community as the exposed group and had a good ascertainment of the outcome. All but one study had a good assessment of the exposure, yet in one study it was not clear if eradication was successful in all patients because of incomplete data.[51] In two studies, the eradicated group was a selected group of individuals (i.e. factory workers).[50,55] One study could not demonstrate that gastric cancer was not present at start.[51] Two studies had a rather short follow-up time, with a mean around 3 years.[52,56] One study had a limited completeness of follow-up (56%) and there was no description of the individuals lost to follow-up,[56] and 1 study had no

statement about follow-up of the cohort members.[53] Four studies reported risk estimates adjusted for time for follow-up and confounding.[50,52,54,56] The confounders adjusted for were not specified in one study,[56] while the other three studies adjusted for age and sex. One study further adjusted for alcohol use, tobacco smoking, and gastric mucosal atrophy,[50] another for the indication for *H. pylori* eradication,[52] and the last one also adjusted for location of peptic ulcer, salt consumption, and tobacco smoking.[54]

### *Helicobacter pylori* eradication therapy and gastric cancer risk

Among 12,899 patients who were successfully eradicated, 119 (0.9%) developed gastric cancer during follow-up, while such cancer was found in 208 out of 18,654 (1.1%) in the non-eradicated group. The pooled analysis of all 8 included studies provided an RR of 0.46 (95% CI 0.32-0.66) in favour of eradication therapy (Figure 2). The heterogeneity was low ($I^2$ 32.3%) and there was no evidence of small study effects or publication bias (p=0.333). When the Finish study was excluded, because of the low incidence of gastric cancer in Finland compared to East-Asian countries, the seven Japanese studies provided a pooled RR of 0.40 (95% CI 0.29-0.54, $I^2$ 0.0%). Another sensitivity analysis excluding the study where a proportion of the participants had intestinal metaplasia at baseline yielded an RR of 0.48 (95% CI 0.34-0.66, $I^2$ 24.2%). The five studies comparing successful versus unsuccessful eradication showed an RR of 0.47 (95% CI 0.31-0.71, $I^2$ 40.9%), and the three studies comparing eradicated with non-eradicated individuals showed an RR of 0.39 (95% CI 0.14-1.08, $I^2$ 49.9%) (Figure 2). The five studies not reporting baseline gastric histopathology (atrophy, intestinal metaplasia or dysplasia) showed an RR of 0.52 (95% CI 0.35-0.77, $I^2$ 35.7%), and the three studies including patients with aberrant baseline histology (gastric atrophy or intestinal metaplasia) showed an RR of 0.28 (95% CI 0.11-0.72, $I^2$ 40.9%) (forest plot not shown). Four studies reported RRs adjusted for follow-up time and confounding, of

which three were analysed using Cox regression and one using Poisson regression, resulting in a pooled adjusted RR of 0.46 (95% CI 0.29-0.72, $I^2$ 44.4%), and 0.33 (95% CI 0.19-0.59) when including only the three studies using Cox regression (Figure 3).

### *Helicobacter pylori* eradication therapy and oesophageal cancer risk

The only study assessing the risk of oesophageal cancer was performed in China, and compared eradication to placebo treatment.[20] The mean age was 42 years (range 35 to 65) and the proportion of men to women was similar in both groups. The eradication rate was 84%. Two out of 817 (0.2%) individuals who received eradication therapy developed oesophageal cancer, compared to 1 out of 813 (0.1%) individuals who received placebo; all three cancers were squamous cell carcinomas.[20]

## Discussion

This meta-analysis indicates that eradication therapy for *H. pylori* prevents gastric adenocarcinoma. The literature is insufficient to allow analysis of the risk of MALT lymphoma or oesophageal cancer following eradication in a meta-analysis.

The main strength of this meta-analysis is that by including only cohort studies we were able to conduct an objective analysis on a large number of participants over a long follow-up period. The eight included studies are based on cohorts close to clinical practice without obvious selection issues. The fact that the studies presenting both unadjusted and adjusted results showed similar effect sizes indicates lack of strong confounding by the factors adjusted for. Also, this study was based on an a priori established study protocol and a thorough systematic search of the literature. Limitations of meta-analyses in general are that the validity is dependent on the quality of the included studies, heterogeneity between studies,

and on possible publication bias. The quality was considered good in seven out of eight studies and moderate in one, the statistical heterogeneity was low to moderate, and there was no evidence of small-study effects bias (publication bias). Moreover, the results were consistent in various sensitivity analyses. Analysis of studies comparing eradicated individuals with individuals not having undergone any attempt to treat the bacteria, and studies comparing eradicated individuals with unsuccessfully eradicated individuals showed similar results. The detection of *H. pylori* and consequent evaluation of success of eradication may have influenced the results, especially in the Finnish study where success of eradication was less clearly defined (a large proportion of patients did not have information regarding cure).[51] Outcome was measured with endoscopy in seven studies and extracted from a cancer registry in one study.[51] In three studies, patients presented with atrophy or intestinal metaplasia at baseline.[50,52,57] There were two studies performed on a selected group, namely male factory workers, who are likely to be healthier than the general population ("healthy worker effect").[58] A limitation was that almost all studies were conducted in Japan, an area with a high incidence of gastric cancer, which questions whether the results are generalizable to non-Asian populations.

The finding that *H. pylori* eradication therapy prevents gastric cancer is in line with the findings of two previous meta-analyses based on randomized clinical trials.[15,16] The relative risk of gastric cancer after eradication therapy compared to placebo or no treatment was 0.66 (95% CI 0.46-0.95) in the most recent meta-analysis, and thus our meta-analysis yielded a stronger preventive effect. The earlier meta-analysis was performed on the same randomized clinical trials, but included data from one randomized clinical trial twice.[16,59] Compared to the most recent meta-analysis, which investigated the risk of gastric cancer after *H. pylori* eradication in healthy asymptomatic individuals in six individual

randomized clinical trials with follow-up ranging from maximum 5 to 14.7 years,[15] the present meta-analysis included studies with a longer follow-up (up to 20 years)[51] and almost four times more treated individuals, and more than five times more controls. Most of the randomized clinical trials included in the previous meta-analyses were conducted in China, leading to a limited generalizability of the results (similar to the present study). Furthermore, cohort studies better resemble clinical practice and reduce selection of participants compared to randomized clinical trials.

There is a debate whether *H. pylori* eradication prevents gastric cancer. There are suggestions that once the histology has reached the level of intestinal metaplasia in the gastric adenocarcinoma development pathway, eradication therapy may no longer have cancer preventive effects.[60] However, it is likely that *H.* pylori eradication lowers the risk of gastric cancer compared to no treatment,[61] which is supported by the findings of the present meta-analysis and the two previous meta-analyses. *H. pylori* is more strongly associated with the risk of intestinal type of gastric adenocarcinoma than with the diffuse type.[62] In one study it was suggested that *H. pylori* eradication would prevent only the intestinal type, because the diffuse type developed only in individuals cured from *H. pylori* infection.[47] In the present study, the results indicate a similarly strong preventive role of eradication for both histological types of gastric adenocarcinoma.

To conclude, this systematic review and meta-analysis of eight cohort studies and 31,553 patients indicates that eradication therapy for *H. pylori* prevents gastric cancer. Research examining *H. pylori* eradication in relation to the risk of gastric MALT lymphoma and oesophageal cancer is currently too limited to enable meta-analyses.

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**Table 1: Patient characteristics of studies included in a meta-analysis of *Helicobacter pylori* eradication and risk of gastric cancer.**

| Study | Males receiving eradication (%) | Male control subjects (%) | Age range among all included individuals (years) | Mean age for those receiving eradication (years) | Mean age among control subjects (years) | Baseline histology of the gastric mucosa |
|---|---|---|---|---|---|---|
| Uemura, 2001 | 57 | NA | 20-76 | 52 | NA | 53% moderate atrophy, 17% severe atrophy<br>37% intestinal metaplasia |
| Kato, 2006 | 66 | 57 | NA | 55 | 53 | Not reported |
| Takenaka, 2007 | 71 | NA | NA | 54 | NA | 5-7% atrophic gastritis |
| Ogura, 2008 | 57 | 55 | NA | 62 | 63 | Not reported |
| Mabe, 2009 | 71 | 71 | NA | 52 | 58 | Not reported |
| Yanaoka, 2009 | 98 | NA | 40-60 | NA | NA | Not reported |
| Kosunen, 2011 | 44 | 44 | NA | 56 | 55 | Not reported |
| Take, 2014 | 89 | NA | 17-83 | 50 | NA | 100% atrophy (mild to severe) |

NA: not available

**Table 2: *Helicobacter pylori* eradication strategy in studies included in a meta-analysis of eradication and risk of gastric cancer.**

| Study | Eradication regimen | Method to detect *H. pylori* | Successful eradication (%) | Control group |
|---|---|---|---|---|
| Uemura, 2001 | Not available | Rapid urease test, histology, serology | not reported | no eradication |
| Kato, 2006 | PPI triple therapy (lansoprazole 60mg, amoxicillin 1500mg and clarithromycin 400mg)<br>2-week combination therapy with PPI and antibiotics | Urea breath test or biopsy-based methods | not reported | unsuccessful eradication |
| Takenaka, 2007 | Triple or dual therapy: amoxicillin 750mg, lansoprazole 30mg or omeprazole 20mg and (clarithromycin 200/400mg for triple therapy) | Urea breath test, rapid urease test, histology, culture, serology | 85% | unsuccessful eradication |
| Ogura, 2008 | 7 days: lansoprazole 30mg, amoxicillin 750 or 1000mg and clarithromycin 400mg or metronidazole 250mg, twice daily | Urea breath test, rapid urease test, histology, culture, serology | 74% | no eradication |
| Mabe, 2009 | 7 days: 30mg lansoprazole or 20mg omeprazole; 750mg amoxicillin and 200 or 400mg clarithromycin, twice daily | Rapid urease test | 65% (ITT), 79% (PP) | unsuccessful eradication |
| Yanaoka, 2009 | 2 weeks: omeprazole 20 mg and amoxicillin 750 or 500mg, twice daily<br>1 week: omeprazole 20 mg; amoxicillin 750mg and clarithromycin 200mg, twice daily | Serology | 87% | no eradication |
| Kosunen, 2011 | Not available | Serology | not reported | unsuccessful eradication |
| Take, 2014 | 2 weeks: amoxicillin 750mg and omeprazole 20mg or lansoprazole 30mg<br>1 week: amoxicillin 750mg; clarithromycin 200mg or 400mg and omeprazole 20mg or lansoprazole 30mg or rabeprazole 10mg<br>1 week: metronidazole 500mg; amoxicillin 750mg or clarithromycin 200mg and omeprazole 20mg or lansoprazole 30mg or rabeprazole 10mg | Rapid urease test, culture | 85% | unsuccessful eradication |

PPI: proton pump inhibitor

ITT: intention to treat, PP: per protocol

**Table 3: Gastric cancer development following *Helicobacter pylori* eradication in a meta-analysis.**

| Study | Country | Participants, treatment group, N | Included in analysis, treatment^, N | Cases of gastric cancer, treatment, N (%) | Type of adenocarcinoma (intestinal/diffuse), treatment, N | Participants, control group (N) | Included in analysis, control (N) | Cases of gastric cancer, control (%) | Type of adenocarcinoma (intestinal/diffuse), control, N | Mean follow-up in years (range), treatment | Mean follow-up in years (range), control |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Uemura, 2001 | Japan | 253 | 253 | 0 (0) | 0 | 993 | 993 | 36 (3.6) | 23/13 | 4.8 | 8.5 |
| Kato, 2006 | Japan | 1788 | 1788 | 23 (1.3) | 19/4 | 1233 | 1233 | 44 (3.6) | 32/12 | 5.9 | 7.7 |
| Takenaka, 2007 | Japan | 2192 | 1519 | 6 (0.4) | 4/2 | 373 | 288 | 5 (1.7) | 4/1 | 3.25 (max. 9.8) | 2.9 |
| Ogura, 2008 | Japan | 853 | 404 | 6 (1.5) | NA | 623 | 304 | 13 (4.3) | NA | 3.2 | 3.1 |
| Mabe, 2009 | Japan | 3781 | 3781 | 47 (1.2) | 35/10* | 352 | 352 | 9 (2.6) | 5/4 | 5.6 (max. 8.0) | 5.2 (max. 8.4) |
| Yanaoka, 2009 | Japan | 852 | 474 | 5 (1.1) | 4/1 | 4924 | 3664 | 55 (1.5) | 36/19 | max. 10 | max. 10 |
| Kosunen, 2011 | Finland | 3650 | 3650 | 11 (0.3) | NA | 11628 | 11628 | 37 (0.3) | NA | 10.4 (max. 20) | 9.3 (max. 20) |
| Take, 2014 | Japan | 1135 | 1030 | 21 (2.0) | 11/10 | 207 | 192 | 9 (4.7) | 8/1 | 9.9 (max 17.4) | 9.9 (max. 17.4) |

NA: not available

*2 cancers of unknown type

^Number of patients included in the analysis after excluding those lost to follow-up.

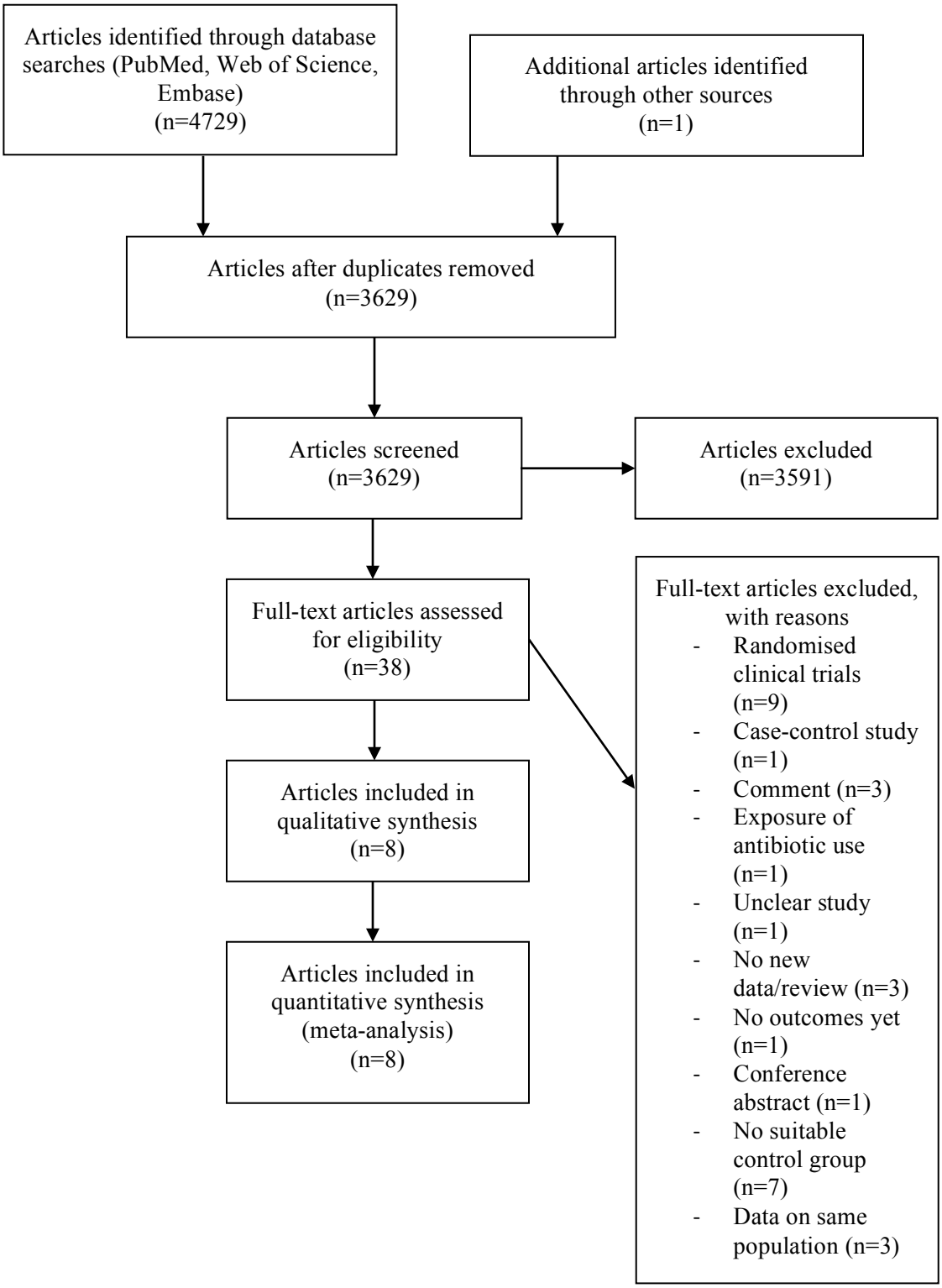


**Figure 1: Flow diagram of study selection adapted from PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) for a meta-analysis assessing gastric cancer risk after *Helicobacter pylori* eradication.**

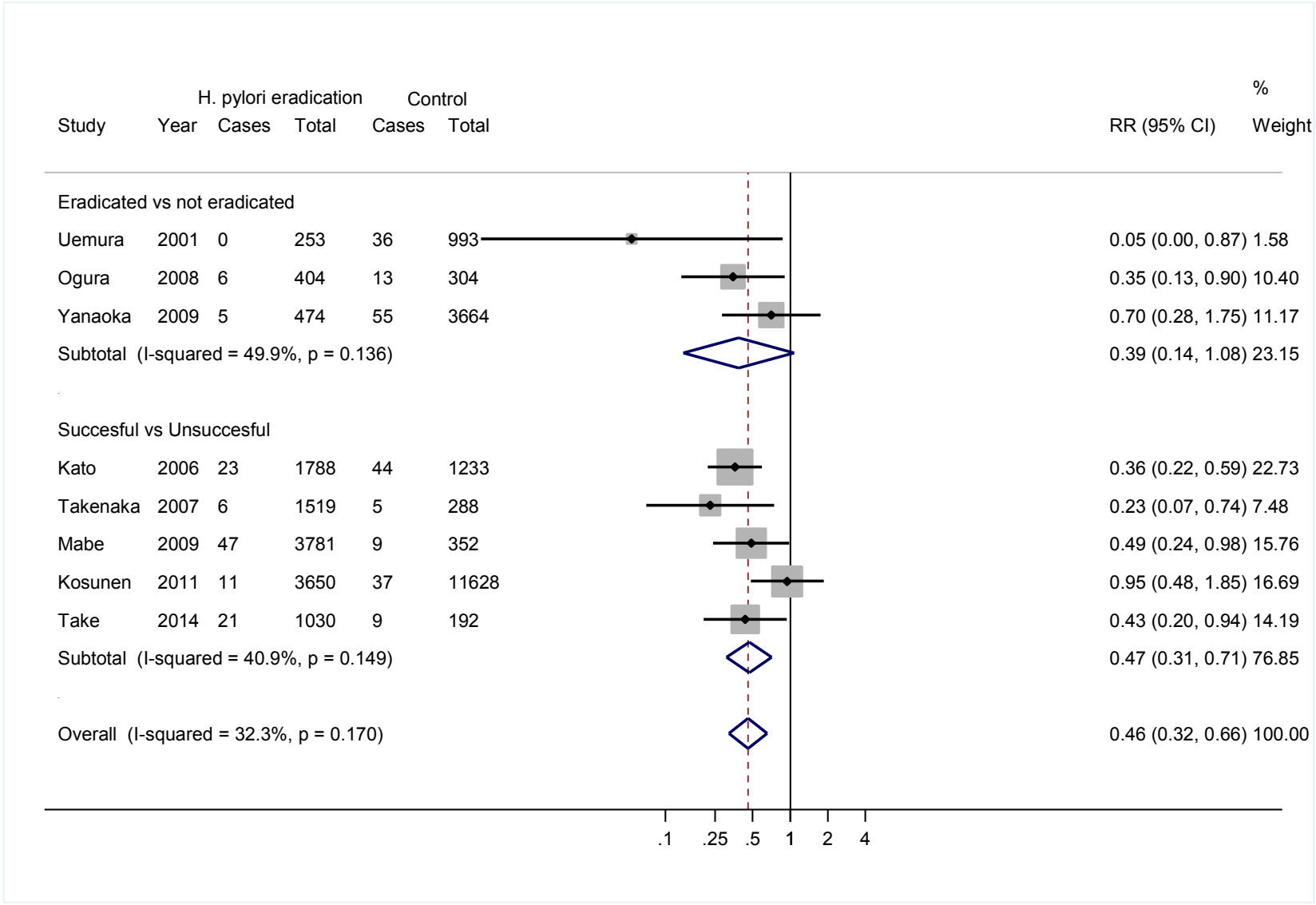


**Figure 2: Forest plot of studies comparing eradication therapy to no treatment and studies comparing successful to unsuccessful treatment. CI, confidence interval; RR, relative risk**

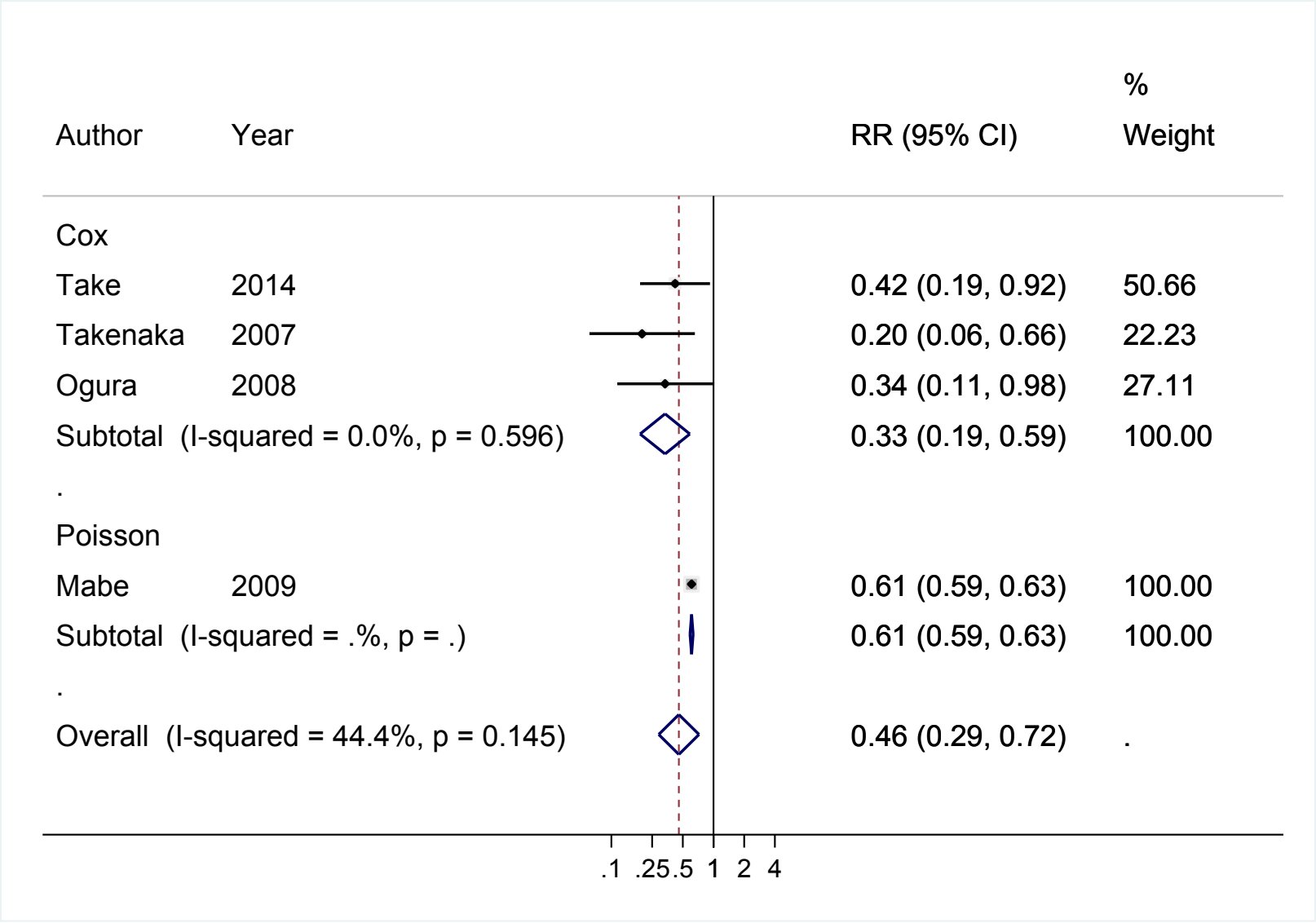


**Figure 3: Forest plot of studies comparing eradicated and not-eradicated groups which reported adjusted values, grouped by Cox or Poisson model. CI, confidence interval; RR, relative risk**

## Appendix: Detailed search strategy of systematic literature search

| *Source* | *Used search terms* | *Settings* | *Articles identified* | *Most recent search* |
|---|---|---|---|---|
| **PubMed (oesophageal)** | (("Helicobacter pylori"[Mesh] OR Helicobacter[tiab] OR pylori[tiab] OR campylobacter[tiab]) AND (eradication[tiab] OR chemoprevention[tiab] OR "proton pump inhibitor" OR PPI OR esomeprazole OR nexium OR omeprazole OR prilosec OR losec OR pantoprazole OR lansoprazole OR rabeprazole OR "histamine H2 antagonists" OR cimetidine OR ranitidine OR famotidine OR nizatidine OR "H2 receptor antagonist" OR H2RA OR "histamine2 receptor antagonist" OR amoxicillin OR bismuth OR clarithromycin OR "macrolides"[Mesh] OR "metronidazole"[Mesh] OR "nitroimidazoles"[Mesh])) AND ("Esophageal Neoplasms"[Mesh] OR (esophag*[tiab] OR oesophag*[tiab]) AND (cancer[tiab] OR carcinoma[tiab] OR neoplas*[tiab] OR tumor[tiab] OR tumour[tiab] OR malignan*[tiab] OR lesion[tiab] OR dysplasia[tiab] OR adenocarcinoma[tiab] OR "squamous cell carcinoma"[tiab])) | | 258 | November 10th, 2015 |
| **Web of Science (oesophageal)** | ('Helicobacter pylori' OR Helicobacter OR pylori OR campylobacter) AND (eradication OR chemoprevention OR 'proton pump inhibitor' OR PPI OR esomeprazole OR nexium OR omeprazole OR prilosec OR losec OR pantoprazole OR lansoprazole OR rabeprazole OR 'histamine H2 antagonists' OR cimetidine OR ranitidine OR famotidine OR nizatidine OR 'H2 receptor antagonist' OR H2RA OR 'histamine2 receptor antagonist' OR amoxicillin OR bismuth OR clarithromycin OR macrolides OR metronidazole OR nitroimidazoles) AND ('Esophageal Neoplasms' OR (esophag* OR oesophag*)) AND (cancer OR carcinoma OR neoplas* OR tumor OR tumour OR malignan* OR lesion OR dysplasia OR adenocarcinoma OR 'squamous cell carcinoma') | In "topic" | 617 | November 10th, 2015 |
| **Embase (oesophageal)** | helicobacter pylori'/exp OR 'helicobacter pylori' OR helicobacter:ab,ti OR pylori:ab,ti OR campylobacter:ab,ti AND (eradication:ab,ti OR chemoprevention:ab,ti OR 'proton pump inhibitor'/exp OR 'proton pump inhibitor' OR ppi OR 'esomeprazole'/exp OR esomeprazole OR 'nexium'/exp OR nexium OR 'omeprazole'/exp OR omeprazole OR 'prilosec'/exp OR prilosec OR 'losec'/exp OR losec OR 'pantoprazole'/exp OR pantoprazole OR 'lansoprazole'/exp OR lansoprazole OR 'rabeprazole'/exp OR rabeprazole OR 'histamine h2 antagonists'/exp OR 'histamine h2 antagonists' OR 'cimetidine'/exp OR cimetidine OR 'ranitidine'/exp OR ranitidine OR 'famotidine'/exp OR famotidine OR 'nizatidine'/exp OR nizatidine OR 'h2 receptor antagonist'/exp OR 'h2 receptor antagonist' OR h2ra OR 'histamine2 receptor antagonist' OR 'amoxicillin'/exp OR amoxicillin OR 'bismuth'/exp OR bismuth OR 'clarithromycin'/exp OR clarithromycin OR 'macrolides'/exp OR 'macrolides' OR 'metronidazole'/exp OR 'metronidazole' OR 'nitroimidazoles'/exp OR 'nitroimidazoles') AND ('esophageal neoplasms'/exp OR 'esophageal neoplasms' OR esophag*:ab,ti OR oesophag*:ab,ti) AND (cancer:ab,ti OR carcinoma:ab,ti OR neoplas*:ab,ti OR tumor:ab,ti OR tumour:ab,ti OR malignan*:ab,ti OR lesion:ab,ti OR dysplasia:ab,ti OR adenocarcinoma:ab,ti OR 'squamous cell carcinoma':ab,ti) | | 557 | November 10th, 2015 |
| **PubMed (gastric)** | (("Helicobacter pylori"[Mesh] OR Helicobacter[tiab] OR pylori[tiab] OR campylobacter[tiab]) AND (eradication[tiab] OR chemoprevention[tiab] OR "proton pump inhibitor" OR PPI OR esomeprazole OR nexium OR omeprazole OR prilosec OR losec OR pantoprazole OR lansoprazole OR rabeprazole OR "histamine H2 antagonists" OR cimetidine OR ranitidine OR famotidine OR nizatidine OR "H2 receptor antagonist" OR H2RA OR "histamine2 receptor antagonist" OR amoxicillin OR bismuth OR clarithromycin OR "macrolides"[Mesh] OR "metronidazole"[Mesh] OR "nitroimidazoles"[Mesh])) AND ("Stomach Neoplasms"[Mesh] OR (stomach[tiab] OR gastric[tiab]) AND (cancer[tiab] OR carcinoma[tiab] OR neoplas*[tiab] OR tumor[tiab] OR tumour[tiab] OR malignan*[tiab] OR lesion[tiab] OR dysplasia[tiab] OR adenocarcinoma[tiab] OR "mucosa associated lymphoid tissue"[tiab] OR MALT[tiab] OR lymphoma[tiab])) | | 2337 | November 10th, 2015 |

| | | | | |
|---|---|---|---|---|
| **Web of Science (gastric)** | ((‘Helicobacter pylori’ OR Helicobacter OR pylori OR campylobacter) AND (eradication OR chemoprevention OR ‘proton pump inhibitor’ OR PPI OR esomeprazole OR nexium OR omeprazole OR prilosec OR losec OR pantoprazole OR lansoprazole OR rabeprazole OR ‘histamine H2 antagonists’ OR cimetidine OR ranitidine OR famotidine OR nizatidine OR ‘H2 receptor antagonist’ OR H2RA OR ‘histamine2 receptor antagonist’ OR amoxicillin OR bismuth OR clarithromycin OR macrolides OR metronidazole OR nitroimidazoles) AND (‘Stomach Neoplasms’ OR (gastric OR stomach)) AND (cancer OR carcinoma OR neoplas* OR tumor OR tumour OR malignan* OR lesion OR dysplasia OR adenocarcinoma OR ‘mucosa associated lymphoid tissue’ OR MALT OR lymphoma)) | In "title" | 456 | November 10th, 2015 |
| **Embase (gastric)** | ‘helicobacter pylori'/exp OR 'helicobacter pylori' OR helicobacter:ti OR pylori:ti OR campylobacter:ti AND (eradication:ti OR chemoprevention:ti OR 'proton pump inhibitor'/exp OR 'proton pump inhibitor' OR ppi OR 'esomeprazole' OR 'esomeprazole'/exp OR esomeprazole OR 'nexium' OR 'nexium'/exp OR nexium OR 'omeprazole' OR 'omeprazole'/exp OR omeprazole OR 'prilosec' OR 'prilosec'/exp OR prilosec OR 'losec' OR 'losec'/exp OR losec OR 'pantoprazole' OR 'pantoprazole'/exp OR pantoprazole OR 'lansoprazole' OR 'lansoprazole'/exp OR lansoprazole OR 'rabeprazole' OR 'rabeprazole'/exp OR rabeprazole OR 'histamine h2 antagonists'/exp OR 'histamine h2 antagonists' OR 'cimetidine' OR 'cimetidine'/exp OR cimetidine OR 'ranitidine' OR 'ranitidine'/exp OR ranitidine OR 'famotidine' OR 'famotidine'/exp OR famotidine OR 'nizatidine' OR 'nizatidine'/exp OR nizatidine OR 'h2 receptor antagonist'/exp OR 'h2 receptor antagonist' OR h2ra OR 'histamine2 receptor antagonist' OR 'amoxicillin' OR 'amoxicillin'/exp OR amoxicillin OR 'bismuth' OR 'bismuth'/exp OR bismuth OR 'clarithromycin' OR 'clarithromycin'/exp OR clarithromycin OR 'macrolides'/exp OR 'macrolides' OR 'metronidazole'/exp OR 'metronidazole' OR 'nitroimidazoles'/exp OR 'nitroimidazoles') AND ('stomach neoplasms'/exp OR 'stomach neoplasms' OR gastric:ti OR stomach:ti) AND (cancer:ti OR carcinoma:ti OR neoplas*:ti OR tumor:ti OR tumour:ti OR malignan*:ti OR lesion:ti OR dysplasia:ti OR adenocarcinoma:ti OR 'mucosa associated lymphoid tissue':ti OR malt:ti OR lymphoma:ti) | | 803 | November 10th, 2015 |
| | | | | |
| ***Additional sources*** | ***Used search terms*** | ***Settings*** | ***Articles identified*** | ***Most recent search*** |
| **Backward- and forwards citation tracking** | Screening reference lists of all selected articles + citation index (Web of Science) | - | 0 | |
| **Cochrane** | Screening PubMed for potentially eligible articles from same authors as selected articles | - | 0 | November 10th, 2015 |